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Review

PaO₂/FiO₂ and SpO₂/FiO₂ ratios revisited: Useful, misleading, or both?Prashant Nasa^{1,2}, Denise Battaglini^{3,4}, Deven Juneja⁵, Marcus J. Schultz^{6,7,8,10},
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ABSTRACT

The ratio of arterial partial pressure of oxygen to the inspired oxygen fraction (PaO₂/FiO₂) serves as a cornerstone metric for the management of patients with acute respiratory distress syndrome (ARDS). This ratio is integral to the Berlin definition of ARDS and is used for severity classification, prognostication, and guiding therapeutic interventions. Furthermore, the PaO₂/FiO₂ ratio has been employed in landmark trials to ascertain patients' eligibility for interventions such as prone positioning and extracorporeal membrane oxygenation. The modifications of the Berlin definition, the Kigali modification, and the 2023 New Global definition suggested using the ratio of peripheral oxygen saturation to FiO₂ (SpO₂/FiO₂) as a surrogate for the PaO₂/FiO₂ ratio when arterial blood gas is inaccessible. Although these oxygenation ratios are valuable for timely recognition and categorizing ARDS, as well as informing clinical decision-making, several significant limitations limit their efficacy, such as dependence on ventilator settings and FiO₂. The isolated use of these oxygenation ratios may not accurately monitor the evolution of the pathology and response to interventions. Additionally, the arbitrary cutoffs established for these oxygenation metrics frequently result in overlapping categories rather than distinct subgroups of ARDS. Finally, pulse oximetry measurements can be compromised by factors such as patient motion, perfusion variability, dyshe-moglobinemia, and skin pigmentation-related bias, which may obscure hypoxemia. Considering these challenges, recent research has explored the trajectory of the PaO₂/FiO₂ ratio relative to static measurements and the reclassification of ARDS severity after 24–48 h for prognostication. Alternative metrics such as the oxygenation index, oxygenation saturation index, and (PaO₂ × 10)/(FiO₂ × PEEP) ratio (which incorporates positive end-expiratory pressure) have demonstrated greater ability to predict patients' outcomes. This review summarizes the evidence base, clinical applications, and pitfalls of PaO₂/FiO₂ and SpO₂/FiO₂ ratios in ARDS and potential alternatives, particularly in the context of diagnosis, categorization, and management of ARDS.

Introduction

Assessment of *gas exchange and hypoxemia* remains a cornerstone of managing critically ill and perioperative patients. For decades, the oxygenation ratio, described as the partial pressure of oxygen (PaO₂) to the fraction of inspired oxygen (FiO₂) (PaO₂/FiO₂ ratio), has guided clinical decisions,

diagnosis, severity classification, research categorization, and guideline development.^[1] Originally conceived for stratification of acute respiratory distress syndrome (ARDS), it is now widely used for treatment escalation, resource allocation, and prognostication of other forms of respiratory failure, far beyond its original scope.^[2] Yet mounting evidence questions this reliance.

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Another oxygenation ratio in which oxygen saturation from a pulse oximeter (SpO_2) replaces PaO_2 , $\text{SpO}_2/\text{FiO}_2$ ratio, has emerged as a noninvasive and feasible alternative, especially in resource-limited settings.^[3] The indices such as $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios offer a *simple, widely applicable, and clinically useful approach* for rapid severity stratification and guiding therapeutic interventions, including in nonspecialist settings. However, oxygenation composite metrics incorporating lung mechanics and gas exchange offer potentially superior insights. Meanwhile, advances in monitoring, such as lung ultrasound and electrical impedance tomography, challenge the assumption that a single-point oxygenation measurements adequately capture the complexity of respiratory failure.^[4]

This review explores the evolution, evidence, and limitations of oxygenation ratios and delves into the emerging oxygenation metrics. As healthcare systems increasingly prioritize resource efficiency and precision-based interventions, the time has come to assess whether our traditional approaches to oxygenation assessment still serve modern clinical practice, or whether a shift toward more comprehensive, precise strategies is needed to optimize patient management and outcomes.

History of Oxygenation Ratios

The first description of ARDS provided by David Ashbaugh in 1967^[5] emphasized the hypoxia that was refractory to conventional oxygen therapy. In 1988, Murray et al.^[6] proposed a Lung Injury Score as an expanded definition that incorporated key pathophysiological features of ARDS. This framework incorporated the $\text{PaO}_2/\text{FiO}_2$ ratio as a component reflecting the severity of lung injury, alongside other parameters such as positive end-expiratory pressure (PEEP), respiratory system compliance, and chest radiographic findings. Furthermore, while a PEEP was included in the Lung Injury Score, it is important to note that the $\text{PaO}_2/\text{FiO}_2$ ratio was scored independently of the PEEP level. The American-European Consensus Conference delineated acute lung injury and ARDS using $\text{PaO}_2/\text{FiO}_2$ ratios of ≤ 300 and < 200 mmHg, respectively.^[7] Notably, this definition also failed to specify ventilator settings, particularly minimum PEEP and FiO_2 levels, at the time of measurement. Ferguson et al.^[8] proposed a minimum PEEP of 10 cmH₂O for the assessment of oxygenation in the first Delphi definition.

Villar et al.^[9] prospectively evaluated different combinations of PEEP and FiO_2 settings in a cohort of patients with ARDS and demonstrated that ventilator settings of $\text{PEEP} \geq 10$ cmH₂O and $\text{FiO}_2 \geq 0.5$ on day 1, were associated with significant difference in intensive care unit (ICU) mortality across categories of acute lung injury, ARDS, and acute hypoxemic respiratory failure (AHRF).^[9] In a separate multicenter prospective study, the severity categorization of ARDS based on $\text{PaO}_2/\text{FiO}_2$ measurements with a $\text{PEEP} \geq 10$ cmH₂O and $\text{FiO}_2 \geq 0.5$ on day 1 was associated with significant differences in mortality across categories.^[10]

Subsequently, the Berlin definition reduced the minimum level of PEEP to 5 cmH₂O for $\text{PaO}_2/\text{FiO}_2$ ratio measurement on the basis of feasibility.^[11] Additionally, the $\text{PaO}_2/\text{FiO}_2$ ratio was used to stratify ARDS into mild (201 to ≤ 300 mmHg), moderate (101 to ≤ 200 mmHg), and severe (≤ 100 mmHg) categories. The thresholds for the $\text{PaO}_2/\text{FiO}_2$ ratio in the New Global definition remain unchanged.^[12]

The $\text{SpO}_2/\text{FiO}_2$ ratio was proposed by Rice et al.,^[13] as an alternative oxygenation ratio for the diagnosis and follow-up of ARDS patients in situations where arterial blood gas (ABG) is unavailable.^[13] The Kigali modification of the Berlin definition of ARDS has also reported a comparative efficacy of the $\text{SpO}_2/\text{FiO}_2$ ratio relative to the $\text{PaO}_2/\text{FiO}_2$ ratio in diagnosing ARDS, based on a single-center study, conducted in a resource-constrained setting of Rwanda.^[14] The new Global definition incorporated $\text{SpO}_2/\text{FiO}_2$ as an alternative to $\text{PaO}_2/\text{FiO}_2$ ratio in resource-limited settings, for the diagnosis of hypoxia and for classification of severity of ARDS, provided the SpO_2 is $\leq 97\%$.^[10]

Evidence on Oxygenation Ratios

The $\text{PaO}_2/\text{FiO}_2$ ratio for defining hypoxemia in ARDS was formally incorporated into the American-European Consensus Conference definition through expert consensus.^[7] The Berlin definition used a Delphi-based consensus process involving an international panel to draft a definition and to propose a $\text{PaO}_2/\text{FiO}_2$ ratio-based categorization of ARDS. The definition and severity categories were validated through a meta-analysis of patient-level datasets from four multicentric clinical trials involving over 4000 patients. The mortality rates, median duration of ventilation, and ventilator-free days were inversely proportional to the $\text{PaO}_2/\text{FiO}_2$ ratios. The thresholds for $\text{PaO}_2/\text{FiO}_2$ ratios were merely developed through consensus for practical considerations in grading outcomes, including mortality, along a continuum, rather than relying on strict physiological inflection points. Therefore, it may seem reasonable to think that the $\text{PaO}_2/\text{FiO}_2$ thresholds are predictive of mortality in ARDS. However, the area under the receiver operating characteristic curve (AUROC) for the Berlin definition was only 0.577 (95% confidence intervals [CI]: 0.561 to 0.593).^[11] Moreover, the Berlin definition does not clearly specify the optimal timing for severity assessment using $\text{PaO}_2/\text{FiO}_2$ ratios (e.g., at admission, within the first 24 h or at the worst point within the first 48 h), nor the extent of ventilator optimization before measurement. This lack of standardization may influence the classification of ARDS severity, as oxygenation indices can vary considerably depending on ventilator settings and the timing of assessment.^[9,10]

A few clinical trials and guidelines have attempted to categorize ARDS using a single $\text{PaO}_2/\text{FiO}_2$ cutoff of 150 mmHg, distinguishing mild-moderate from moderate-severe disease.^[15–17] Notably, several landmark ARDS trials, including those evaluating neuromuscular blockade and prone positioning, have used a $\text{PaO}_2/\text{FiO}_2$ threshold of 150 mmHg for patient selection.^[15,16] Moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$ mmHg) had worse physiological and anatomical derangements (such as peak pressure, arterial partial pressure of carbon dioxide [PaCO_2], pH, heavier lungs, and greater inhomogeneity), greater lung recruitability and higher mortality risk compared with mild-moderate ARDS ($\text{PaO}_2/\text{FiO}_2$ 150 to ≤ 300 mmHg).^[18] Yet, the accuracy of $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg for predicting mortality was low with an AUROC of 0.56 (95%CI: 0.51 to 0.61).^[19]

The $\text{SpO}_2/\text{FiO}_2$ ratio derived from pulse oximetry possesses inherent advantages such as non-invasiveness, continuous, ease of availability, and affordability and is a fair surrogate of PaO_2 , with $\text{SpO}_2/\text{FiO}_2$ ratios of 315 and 235 cor-

Table 1Adult studies showing prediction of PaO₂/FiO₂ from SpO₂/FiO₂ ratios.

Authors	Patient population	Sample size	Correlation between SpO ₂ /FiO ₂ and PaO ₂ /FiO ₂	Statistical results
Rice et al. ^[13]	ARDS patients under MV	672 for derivation and 402 for validation	SpO ₂ /FiO ₂ =235 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =315 indicated PaO ₂ /FiO ₂ =300	NA
Tripathi et al. ^[26]	Patients on IMV as a part of general anesthesia	2754	SpO ₂ /FiO ₂ =206 indicated PaO ₂ /FiO ₂ =300 SpO ₂ /FiO ₂ =180 indicated PaO ₂ /FiO ₂ =200	NA
Namendys-Silva et al. ^[27]	All ICU patients	232	SpO ₂ /FiO ₂ ≤ 512 indicating PaO ₂ /FiO ₂ ≤ 400 SpO ₂ /FiO ₂ ≤ 357 indicating PaO ₂ /FiO ₂ ≤ 300 SpO ₂ /FiO ₂ ≤ 214 indicating PaO ₂ /FiO ₂ ≤ 200 SpO ₂ /FiO ₂ ≤ 89 indicating PaO ₂ /FiO ₂ ≤ 100	NA
Serpa Neto et al. ^[28]	Patients with sepsis	260	SpO ₂ /FiO ₂ =154 indicated PaO ₂ /FiO ₂ =100 SaO ₂ /FiO ₂ =241 indicated PaO ₂ /FiO ₂ =300	NA
Schmidt et al. ^[29]	All patients under MV	3767	SpO ₂ /FiO ₂ =295 indicated PaO ₂ /FiO ₂ ≤ 300	99% sensitivity and 9.9% specificity
Bass et al. ^[30]	Patients with ARF under MV	77	SpO ₂ /FiO ₂ ≤ 315 indicated PaO ₂ /FiO ₂ ≤ 300 SpO ₂ /FiO ₂ ≤ 235 indicated PaO ₂ /FiO ₂ ≤ 200	Sensitivity of 83% and specificity of 50% Sensitivity of 70% and specificity of 90%
Bashar et al. ^[31]	ICU post-operative after CABG	175 for derivation and 358 for validation	SpO ₂ /FiO ₂ =311 indicated PaO ₂ /FiO ₂ =300	Sensitivity of 90% and specificity of 80%
Babu et al. ^[32]	Respiratory failure admitted in surgical ICU	300	SpO ₂ /FiO ₂ =285 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =323 indicated PaO ₂ /FiO ₂ =300	Sensitivity of 73% and specificity of 77% Sensitivity of 72% and specificity of 73%
Kumar et al. ^[33]	ARF admitted in COVID ICU	80	SpO ₂ /FiO ₂ =219 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =299 indicated PaO ₂ /FiO ₂ =300	NA
Gandhi et al. ^[34]	Respiratory failure admitted in COVID ICU	100	SpO ₂ /FiO ₂ =205 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =290 indicated PaO ₂ /FiO ₂ =300	NA
Choudhury et al. ^[35]	COVID-19 patients admitted to ICU	396	SpO ₂ /FiO ₂ =395 indicated PaO ₂ /FiO ₂ =100 SpO ₂ /FiO ₂ =405 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =411 indicated PaO ₂ /FiO ₂ =300	Sensitivity of 66.7% and specificity of 73.5% Sensitivity of 71.8% and specificity of 70.8% Sensitivity of 65% and specificity of 80%
Alur et al. ^[36]	ICU patients with AHRF	125	SpO ₂ /FiO ₂ =252 indicated PaO ₂ /FiO ₂ =200 SpO ₂ /FiO ₂ =321 indicated PaO ₂ /FiO ₂ =300	Sensitivity of 69% and specificity of 95%

AHRF, Acute hypoxic respiratory failure; ARDS, Acute respiratory distress syndrome; ARF, Acute respiratory failure; CABG, Coronary artery bypass grafting; ICU, Intensive care unit; MV, Mechanical ventilation; PaO₂/FiO₂, Partial pressure of arterial oxygen by fraction of inspired oxygen; SpO₂/FiO₂, Oxygen saturation by fraction of inspired oxygen.

responding to PaO₂/FiO₂ ratios of 300 mmHg (91% sensitivity, 56% specificity) and 200 mmHg (86% sensitivity, 85% specificity).^[20] However, the relationship between SpO₂ and PaO₂ is nonlinear and becomes inaccurate above 96% because of the flat portion of oxyhemoglobin curve.^[13] In a large mixed cohort with AHRF including pneumonia, Rice et al.,^[13] found that SpO₂/FiO₂=235 corresponded to PaO₂/FiO₂=200, and SpO₂/FiO₂=315 to PaO₂/FiO₂=300. The study reported a strong correlation between SpO₂/FiO₂ ratio and PaO₂/FiO₂ ratio, demonstrating a linear relationship described by the equation^[13]:

$$\text{SpO}_2/\text{FiO}_2 = 64 + 0.84(\text{PaO}_2/\text{FiO}_2)$$

However, the misclassification of ARDS severity persisted in about 30% of cases. The authors emphasized that FiO₂ standardization is critical for reliable interpretation.^[13] The correlation was further supported by a secondary analysis of the National Heart, Lung, and Blood Institute ARDS Network trials.^[21–23] Additionally, secondary analysis of prospective observational study on COVID-19-related ARDS indicated a good correlation between SpO₂/FiO₂ or PaO₂/FiO₂ ratios in predicting patient outcomes.^[24] Moreover, imputed SpO₂/FiO₂ values corresponding to PaO₂/FiO₂ ratios have also been validated within the *Sequential Organ Failure Assessment (SOFA) score* and have been shown to predict *clinical outcomes*^[25] (Table 1).

Oxygenation Ratios Beyond ARDS

The PaO₂/FiO₂ ratio serves as a gold standard for assessing the severity of hypoxemia for ARDS. However, clinicians increasingly use the PaO₂/FiO₂ ratio and ARDS severity thresholds (e.g., PaO₂/FiO₂ ≤ 300 or ≤ 200 mmHg) in other contexts such as pneumonia, sepsis, perioperative care, and determining the need for respiratory supports like high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV). Moreover, the severity of hypoxemia has been shown to be an independent predictor of mortality in critically ill patients, regardless of the underlying etiology.^[37] Furthermore, SpO₂/FiO₂ ratio is used as an alternative to PaO₂/FiO₂ ratio in many of these conditions, where ABG analysis access is limited.

Pneumonia

The PaO₂/FiO₂ ratio has been used in patients with community-acquired pneumonia (CAP) to determine the severity of hypoxemia, to assess the need for respiratory support, and to predict the outcomes.^[38] Clinical risk scores such as SMART-COP, which includes the PaO₂/FiO₂ ratio, are valuable in predicting the severity of CAP and the need for respiratory or vasopressor support.^[39] The oxygenation indices can also support clinical decision-making by helping to guide the escalation of respiratory support and monitor response to therapy.

Table 2Comparison of respiratory scoring criteria ($\text{PaO}_2/\text{FiO}_2$) between SOFA and SOFA-2.

Score	SOFA	SOFA-2
0	≥ 400 mmHg (53.3 kPa)	> 300 mmHg (> 40.0 kPa) or $\text{SpO}_2/\text{FiO}_2 > 300$ mmHg
1	< 400 (53.3)	≤ 300 mmHg (≤ 40.0 kPa) or $\text{SpO}_2/\text{FiO}_2 \leq 300$ mmHg
2	< 300 mmHg (40.0 kPa)	≤ 225 mmHg (≤ 30.0 kPa) or $\text{SpO}_2/\text{FiO}_2 \leq 250$ mmHg
3	< 200 mmHg (26.7 kPa) with respiratory support	≤ 150 mmHg (≤ 20.0 kPa) and advanced ventilator support or $\text{SpO}_2/\text{FiO}_2 \leq 200$ mmHg
4	< 100 mmHg (13.3 kPa) with respiratory support	≤ 75 mmHg (≤ 10.0 kPa) and advanced ventilator support or ECMO or $\text{SpO}_2/\text{FiO}_2 \leq 120$ mmHg

ECMO, Extracorporeal membrane oxygenation; $\text{SaO}_2/\text{FiO}_2$, Oxygen saturation by fraction of inspired oxygen; SOFA, Sepsis-related organ failure assessment.

Furthermore, worsening hypoxemia, as reflected by declining $\text{PaO}_2/\text{FiO}_2$ ratios, may identify patients at increased risk of progression to ARDS, particularly when invasive ventilation becomes necessary.^[40] Collectively, these observations highlight the importance of oxygenation indices not only in severity assessment but also in anticipating disease trajectory in pneumonia.

The noninvasive nature of $\text{SpO}_2/\text{FiO}_2$ made it valuable, especially where ABGs were limited. In adult pneumonia patients, both COVID-19 and non-COVID-19 related, contemporaneous $\text{SpO}_2/\text{FiO}_2$ and $\text{PaO}_2/\text{FiO}_2$ ratios correlate moderately to strongly, but clinically relevant dispersion limits their interchangeability.^[33,41] However, wide prediction intervals shown in other settings may reduce their standalone reliability. One multicenter study of patients with COVID-19 pneumonia across wards and ICUs demonstrated that $\text{SpO}_2/\text{FiO}_2$ could be used as a surrogate of $\text{PaO}_2/\text{FiO}_2$ ratio in patients and could be highly useful in resource-limited settings during this COVID-19 pandemic. However, the initial $\text{SpO}_2/\text{FiO}_2$ ratio on admission could not indicate the need for invasive ventilation.^[42]

In pneumonia (COVID-19 and non-COVID-19), $\text{SpO}_2/\text{FiO}_2$ provides a practical, noninvasive screening and trending tool. It correlates with $\text{PaO}_2/\text{FiO}_2$ but with a risk of clinically relevant misclassification at decision thresholds. For research eligibility, prognosis, or ventilator management, the $\text{PaO}_2/\text{FiO}_2$ ratio is preferable due to greater precision. For triage and early recognition of deterioration, the $\text{SpO}_2/\text{FiO}_2$ ratio is acceptable, with the caveat that $\text{SpO}_2 > 97\%$ blunts its reliability due to a plateau in the oxyhemoglobin curve.

Sepsis and septic shock

The $\text{PaO}_2/\text{FiO}_2$ ratio is important for the diagnosis of sepsis as a variable of the SOFA score. The cutoffs of the $\text{PaO}_2/\text{FiO}_2$ ratio used in SOFA were also similar to those for severity grading of ARDS, with a higher score for a low $\text{PaO}_2/\text{FiO}_2$. However, the thresholds for the $\text{PaO}_2/\text{FiO}_2$ ratio were changed in the SOFA-2 score (Table 2). Although, the accuracy of predicting mortality for overall SOFA-2 (AUROC 0.79, 95%CI: 0.76 to 0.81) was similar to SOFA (AUROC 0.77, 95%CI: 0.74 to 0.81), the revised cutoffs using 10 kPa (75 mmHg) intervals for $\text{PaO}_2/\text{FiO}_2$ ratio, outperformed the respiratory SOFA score (AUROC 0.615, 95%CI: 0.607 to 0.622 vs. AUROC 0.610, 95%CI: 0.603 to 0.618).^[43–45] Additionally, lower $\text{PaO}_2/\text{FiO}_2$ (< 300 mmHg) ratios have been shown to be independently associated with increased mortality in patients with sepsis.^[46] In a retrospective analysis of MIMIC-IV database, the relationship between $\text{PaO}_2/\text{FiO}_2$ ratio and mortality was U-shaped and $\text{PaO}_2/\text{FiO}_2$ ratios between 183 and

219 mmHg were found to be associated with a lower risk of 28-day mortality.^[47]

SOFA-2 score also incorporates corresponding $\text{SpO}_2/\text{FiO}_2$ ratios when ABG is unavailable. Peripheral perfusion abnormalities associated with worsening shock, due to vasoconstriction or low pulsatility, could be a major concern. Although a low $\text{SpO}_2/\text{FiO}_2$ ratio at ICU admission in patients with sepsis and septic shock was associated with increased mortality risk, especially the lower values; the correlation with the $\text{PaO}_2/\text{FiO}_2$ ratio was only moderate ($r = 0.48$).^[28] In another study in the emergency department, pulse oximetry overestimated arterial oxygen saturation (SaO_2) measured by ABG in patients with severe sepsis or septic shock, with larger errors at lower saturations.^[48] Hence, in sepsis, $\text{PaO}_2/\text{FiO}_2$ is more reliable when obtainable. If $\text{SpO}_2/\text{FiO}_2$ has to be used as a noninvasive alternative, SpO_2 should be kept $< 97\%$, and near decision thresholds should be interpreted cautiously.^[49]

Pulmonary embolism

The $\text{PaO}_2/\text{FiO}_2$ ratio has been used for risk stratification in patients with pulmonary embolism and for identifying patients with a higher risk of deterioration.^[50] The $\text{PaO}_2/\text{FiO}_2$ ratio < 265 mmHg has been identified as an increased risk of in-hospital death, though other studies suggest slightly different cutoffs.^[51] Furthermore, the $\text{PaO}_2/\text{FiO}_2$ ratio has been used to estimate the severity of pulmonary artery obstruction, as it is negatively correlated with the pulmonary artery computed tomography obstruction index. A lower $\text{PaO}_2/\text{FiO}_2$ ratio corresponds to a more severe obstruction.^[52] Although the $\text{PaO}_2/\text{FiO}_2$ ratio may correlate with severity in pulmonary embolism, oxygenation parameters alone do not play a pivotal role in therapeutic decision-making, which is primarily guided by hemodynamic status, right ventricular function, and cardiac biomarkers.

Perioperative and anesthesia settings

In the operating room and postanesthetic care unit, FiO_2 delivery fluctuates rapidly, and lung mechanics change with anesthesia and recruitment. Intra or postoperative oxygenation is confounded by high FiO_2 , variable PEEP, atelectasis, and recruitment manoeuvres—factors that can acutely swing $\text{PaO}_2/\text{FiO}_2$ without reflecting intrinsic lung pathology. These factors limit the reliability of both $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ thresholds derived from resting or ventilated ARDS populations. Although perioperative studies exist for $\text{PaO}_2/\text{FiO}_2$ ratio,^[53] or comparing oxygen reserve index vs. SpO_2 for hypoxemia detection, they generally support pulse oximetry for trend monitoring, but not for applying ARDS-based cutoffs.^[54]

Oxygenation Ratios with Respiratory Support

Respiratory support modalities, such as HFNO, continuous positive airway pressure, bilevel positive airway pressure, NIV, invasive mechanical ventilation, or long-term home ventilation, are often used in the management of respiratory failure. The use of $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios with these modalities is influenced by the settings and PEEP levels.

Estimation of FiO_2 during conventional oxygen therapy can be challenging, particularly when oxygen is delivered via standard face masks or nasal canula. FiO_2 is commonly estimated using conversion tables based on oxygen flow rates. However, the actual delivered FiO_2 can vary considerably when estimated by these equations, depending on factors such as the patient's inspiratory flow, breathing pattern, and mask fit, and consequently exaggerate the severity of hypoxemia, calculated by $\text{PaO}_2/\text{FiO}_2$ or $\text{SpO}_2/\text{FiO}_2$ ratios.^[55] This methodological limitation should be considered when interpreting studies comparing different noninvasive respiratory support strategies.

High-flow nasal oxygen

In HFNO, FiO_2 delivery is more stable at higher flows but still affected by mouth opening, patient inspiratory demand, respiratory rate, and nasal prong fit. Moreover, the physiological benefits of HFNO are due to flow-dependent positive nasopharyngeal pressure, expiratory resistance (PEEP), thereby reducing respiratory rate and effort. However, the benefits are dependent on the patients' ability to close their mouths while on HFNO.^[56–58] Thus variable FiO_2 and PEEP delivery may perturb both $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios, independently of underlying disease severity. This leads to greater heterogeneity and overestimation of ARDS severity.^[59] Consequently, $\text{PaO}_2/\text{FiO}_2$ ratio thresholds established in invasively ventilated patients with ARDS cannot be directly extrapolated to this population. Nevertheless, the oxygenation indices retain clinical relevance under HFNO, as lower values remain associated with worse outcomes, reflecting more severe hypoxemia and disease burden. When ABGs are sparse, $\text{SpO}_2/\text{FiO}_2$ trends and composite indices that incorporate respiratory rate ($\text{ROX index} = [\text{SpO}_2/\text{FiO}_2]/\text{respiratory rate}$) may be useful, but absolute cutoffs beyond ARDS (e.g., $\text{SpO}_2/\text{FiO}_2$ 235/315) translate poorly; device- and patient-specific FiO_2 variability widens error bands.

Noninvasive ventilation

NIV introduces additional uncertainty concerning the FiO_2 delivery due to potential leaks and air entrainment at the interface. These factors can significantly lower the delivered FiO_2 and thereby distorting the oxygenation ratios. Both Bench and clinical studies have demonstrated that the presence of leaks can result in a considerable reduction in FiO_2 and risk overestimation of oxygenation status.^[55,60] In the post hoc analysis of the LUNG SAFE study, the severity assessment by $\text{PaO}_2/\text{FiO}_2$ ratio on NIV was associated with greater intensity of ventilatory support and higher ICU mortality compared to patients on invasive ventilation, particularly among those with a $\text{PaO}_2/\text{FiO}_2 < 150$ mmHg.^[61] Nevertheless, $\text{SpO}_2/\text{FiO}_2$ -based rules yield important prognostic information in patients with mixed-etiology

AHRF on NIV, with a low $\text{SpO}_2/\text{FiO}_2$ ratio is indicative of higher likelihood of NIV failure.^[62]

Limitations and Challenges with Oxygenation Ratios

The ongoing pursuit of an ideal oxygenation matrix in the context of AHRF and ARDS remains a critical area of research. Each index has unique advantages and limitations, and its application may be influenced not only by its inherent limitations but also by a multitude of patient and institutional factors. Consequently, it is imperative to judiciously evaluate these factors when designing or interpreting the results of any clinical trial or translating the evidence at the bedside for decision-making.

Traditionally, the $\text{PaO}_2/\text{FiO}_2$ ratio has been used for the diagnosis, management, and prognostication of ARDS.^[2,11] For most clinical situations, the $\text{PaO}_2/\text{FiO}_2$ ratio remains the gold standard in the management of AHRF. The $\text{PaO}_2/\text{FiO}_2$ ratio cutoff for categorizing ARDS was, however, challenged by many dataset analyses, especially the threshold of 300 mmHg.^[63,64] A recent updated meta-analysis of 28 clinical trials involving 38,270 patients reported a lower accuracy of the $\text{PaO}_2/\text{FiO}_2$ ratio in predicting mortality for patients with ARDS and recommended that the ratio may not be suitable for use as a sole clinical prognostic tool. They reported an AUROC of 0.60 (95%CI: 0.58 to 0.64) for $\text{PaO}_2/\text{FiO}_2$ of 100 mmHg, with a pooled sensitivity and specificity of 44.8% (95%CI: 38.1 to 51.7%), and 70.6% (95%CI: 65.9 to 74.9%), respectively. In contrast, for a $\text{PaO}_2/\text{FiO}_2$ ratio of 200 mmHg, the AUROC was 0.64 (95%CI: 0.60 to 0.69), with pooled sensitivity and specificity of 83.9% (95%CI: 78.9 to 87.8%) and 26.1% (95%CI: 20.8 to 32.1%), respectively.^[65]

The $\text{PaO}_2/\text{FiO}_2$ ratio is affected by various factors such as switching from non-invasive to invasive mechanical ventilation and ventilatory settings, for example, PEEP, FiO_2 , mean airway pressure, and minute ventilation. An important limitation of the $\text{PaO}_2/\text{FiO}_2$ ratio is its nonlinear relationship with FiO_2 , whereby changes in FiO_2 can lead to disproportionate and sometimes misleading changes in the $\text{PaO}_2/\text{FiO}_2$ ratio, independent of true alterations in pulmonary gas exchange. This phenomenon reflects the complex interplay between ventilation-perfusion mismatch, shunt fraction, and oxygen-hemoglobin dissociation curve.^[66] As a result, identical $\text{PaO}_2/\text{FiO}_2$ ratios may represent different degrees of lung injury at varying FiO_2 levels, limiting their reliability as a standalone marker of disease severity. The nonlinear $\text{PaO}_2/\text{FiO}_2$ - FiO_2 relationship underscores the need to interpret the $\text{PaO}_2/\text{FiO}_2$ ratio within the broader clinical and ventilatory context. The dependence on FiO_2 may also diminish the utility of these indices, as FiO_2 can be influenced by various factors, such as mode of oxygen delivery (nasal prongs, face mask, HFNO, NIV, or invasive mechanical ventilation) and ventilatory settings.^[49]

Moreover, $\text{PaO}_2/\text{FiO}_2$ requires arterial sampling, which is invasive, painful, and may not be readily available, especially in resource-limited settings. It also requires technical expertise, and its processing requires special apparatus, which is expensive, needs maintenance, and is not widely available. It may not be possible to store and transport ABG samples, as this may affect PaO_2 readings.^[2]

The $\text{SpO}_2/\text{FiO}_2$ ratio has been suggested as a potential surrogate and may be particularly useful in situations where

ABG sampling is unavailable or not feasible.^[11,67] The seminal ARDS work that popularized $\text{SpO}_2/\text{FiO}_2$ cutoffs cautioned about its use at high saturations.^[13] The correlation between $\text{SpO}_2/\text{FiO}_2$ and $\text{PaO}_2/\text{FiO}_2$ ratios has been evaluated in several recent studies.^[13,28,29,33,68,69] Despite numerous studies, the correlation between $\text{PaO}_2/\text{FiO}_2$ and $\text{SpO}_2/\text{FiO}_2$ ratios, is moderate to strong.^[26,32,34,70] Moreover, the oxyhemoglobin curve plateaus above $\text{SpO}_2 > 96\%$, and imputation of $\text{PaO}_2/\text{FiO}_2$ from $\text{SpO}_2/\text{FiO}_2$ may become inaccurate.^[71] Therefore, different $\text{SpO}_2/\text{FiO}_2$ thresholds have been identified across studies, and different equations have been proposed for imputing $\text{PaO}_2/\text{FiO}_2$ from $\text{SpO}_2/\text{FiO}_2$.^[26,36,72] The challenges exist in using $\text{SpO}_2/\text{FiO}_2$ and $\text{PaO}_2/\text{FiO}_2$ interchangeably, especially at higher FiO_2 , and in monitoring the severity and progression of ARDS.^[68,70,73] Imprecision of the SpO_2 measurement and these equations may lead to misclassification of ARDS based on the $\text{SpO}_2/\text{FiO}_2$ ratio, which could be as high as 33% of patients. Moreover, the accuracy does not improve with dynamic monitoring of the $\text{SpO}_2/\text{FiO}_2$ ratio.^[72] Therefore, panelists from a recent international Delphi study on defining and subphenotyping ARDS expressed reservations regarding the routine implementation of the $\text{SpO}_2/\text{FiO}_2$ ratio, and indicated the need for further validation before its acceptance in future ARDS definitions.^[73]

Furthermore, several other factors may also limit the clinical applicability of the $\text{SpO}_2/\text{FiO}_2$ ratio.^[2,49] The $\text{SpO}_2/\text{FiO}_2$ ratio is dependent on pulse oximetry readings, which can be influenced by various factors such as anemia, skin color, carbon monoxide intoxication, methemoglobinemia, certain dyes and pigments (e.g., nail polish), hyperbilirubinemia, hypoperfusion, high venous pressure, hypoxemia, and hyperoxia.^[49] Moreover, pulse oximetry was associated with greater occult hypoxemia and can artifactually inflate the $\text{SpO}_2/\text{FiO}_2$ ratio, particularly in darker-skinned patients.^[74] The hidden hypoxia was particularly higher among Black individuals and those of African American ethnic background.^[75] Moreover, this overestimation of oxygen saturation translates into health disparities with delayed treatment and higher readmission to the hospital among patients with dark-skin pigmentation.^[76] Even excessive patient movements can impact the accuracy of pulse oximetry readings. Given the common presence of these factors in critically ill patients, the validity of pulse oximetry readings may be compromised.

Beyond oxygenation ratios

Although oxygenation indices are surrogates of lung injury severity and are valuable in clinical decision-making, their interpretation is influenced by the complex interplay of ventilation-perfusion mismatch, shunt fraction, and the level and type of respiratory support provided. As a result, patients with markedly different pathophysiological profiles may have similar $\text{PaO}_2/\text{FiO}_2$ ratios, thereby complicating risk stratification and limiting treatment precision.^[66] Despite the ease of use of oxygenation ratios, their limitations are becoming increasingly recognized. Several additional or complementary metrics have been made available to support a more comprehensive evaluation of respiratory function, potentially better capturing the interactions among oxygenation, lung mechanics, and ventilator settings. We have categorized these indices into: those readily available at bedside and do not require advanced ven-

tilatory maneuvers; those requiring specific ventilatory maneuvers/calculations, and those requiring additional devices.

Indices not Requiring Specific Ventilator Maneuvers

$\text{PaO}_2/\text{FiO}_2$ ratio does not account for airway pressures, and thus, investigators included PEEP as the $(\text{PaO}_2 \times 10) / (\text{FiO}_2 \times \text{PEEP})$ ratio,^[77] or mean airway pressure as an oxygenation factor,^[78] as more integrative metrics. Both indices have been shown to be superior in predicting severity and patient outcomes.

Oxygenation factor = $\text{PaO}_2/\text{FiO}_2/\text{Paw}$, where Paw is the mean airway pressure.

Similarly, oxygenation index $(\text{Paw} \times 100 \times \text{FiO}_2/\text{PaO}_2)$ and surrogate oxygen saturation index $(\text{Paw} \times 100 \times \text{FiO}_2/\text{SpO}_2)$ incorporating mean airway pressure have been found to be superior predictors of outcomes than traditional oxygenation ratios.^[79,80]

The dynamic trajectory of the $\text{PaO}_2/\text{FiO}_2$ ratio or reclassification of severity after 24–48 h has also been found to be a better predictor of prognosis, response to interventions such as PEEP, and patient outcomes than static measurements.^[81–83]

Indices Requiring Specific Ventilatory Maneuvers or Calculations

Lung compliance and elastance, calculated from plateau pressure and tidal volume, reflect the respiratory system's mechanical properties. Lower compliance and higher elastance frequently suggest more severe lung parenchymal involvement or atelectasis, and are independently linked with death.^[84] Combining oxygenation indices and compliance (for example, the “oxygenation-compliance index”) may aid in the identification of patients with recruitable lung tissue or different physiological phenotypes.^[85,86] For example, two patients with equal $\text{PaO}_2/\text{FiO}_2$ ratios may differ significantly in compliance—one with recruitable atelectasis, the other with fixed fibrotic change—implying very different responses to PEEP or prone positioning (Figure 1).

Similarly, the dead space fraction (Vd/Vt) measures ventilation efficiency and pulmonary perfusion. Elevated dead space can be caused by alveolar overdistension, microvascular obstruction, or thrombotic complications, none of which are reflected in oxygenation measurements. Increased Vd/Vt has been repeatedly linked to poor outcomes in ARDS and may act as a surrogate for pulmonary vascular dysfunction, supplementing oxygenation-based measurements.^[87,88] Surrogates, such as the ventilatory ratio (VR)^[89] or the $\text{PaCO}_2/\text{end-tidal carbon dioxide (etCO}_2)$ gradient, can be used at the bedside when direct measures of dead space are unavailable.^[90–92]

The shunt fraction is the proportion of cardiac output that perfuses nonventilated regions and directly quantifies the severity of intrapulmonary shunt. Although perfect estimation necessitates invasive sampling or numerous gas measurements, simple calculations using alveolar gas equations can approximate the shunt fraction. Integrating shunt, dead space, and compliance data may assist in distinguishing “low-compliance, high-shunt” from “high-compliance, high-dead-space” phenotypes, which respond differently to PEEP, recruitment, or prone positioning.^[92,93]

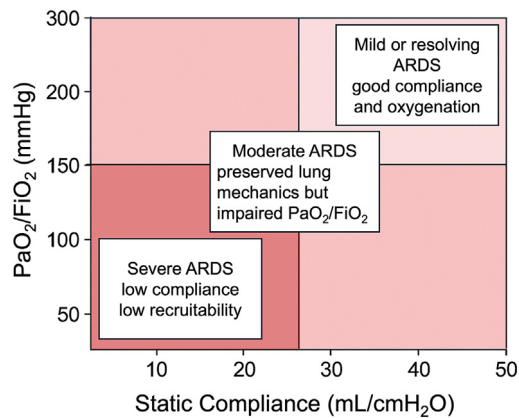


Figure 1. Relationship between oxygenation indices and respiratory system compliance to define physiological phenotypes in ARDS. The figure illustrates the relationship between oxygenation and static compliance, highlighting that patients with similar $\text{PaO}_2/\text{FiO}_2$ ratios may have markedly different respiratory mechanics, reflecting distinct underlying pathophysiology. Three representative phenotypes are shown: $\text{PaO}_2/\text{FiO}_2$ with preserved compliance (recruitable atelectasis), suggesting potentially recruitable lung units despite impaired oxygenation; low $\text{PaO}_2/\text{FiO}_2$ with low compliance (fibrotic or nonrecruitable lung), consistent with severe, poorly recruitable lung injury; and preserved $\text{PaO}_2/\text{FiO}_2$ with high compliance, representing mild or resolving disease. Integrating oxygenation and compliance offers a more comprehensive, physiology-based assessment of ARDS, enabling better phenotyping and more individualized ventilatory management than either parameter alone. ARDS, Acute respiratory distress syndrome; $\text{PaO}_2/\text{FiO}_2$, Partial pressure of oxygen to fraction of inspired oxygen. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Recent research has examined composite measures that combine oxygenation and mechanics. The “oxygenation–ventilation index,” “mechanical power,” and “stress index” take into account pressure–volume relationships, respiratory rate, and driving pressure to measure both the efficiency and potential harm caused by mechanical ventilation. These multidimensional metrics better reflect the interactions among gas exchange, mechanics, and ventilator settings, improving predictive power and therapy personalization.^[94,95]

Indices Requiring Additional Devices

Beyond traditional physiological parameters, innovative monitoring technologies provide novel insights into regional and dynamic variation. Electrical impedance tomography (EIT) provides for continuous bedside monitoring of regional ventilation and, with newer algorithms, perfusion distribution. EIT can assess regional compliance and detect overdistension or collapse during PEEP titration, bridging the gap between global indices and regional physiology. Lung ultrasound and quantitative CT help to characterize aeration and recruitability, while newer techniques such as functional lung MRI or dual-energy CT allow for noninvasive measurement of ventilation–perfusion mismatch and shunt percentage. Integrating these imaging modalities with standard measurements has the potential to reinvent severity classification, shifting away from static thresholds (such as $\text{PaO}_2/\text{FiO}_2$ cutoffs) toward physiologically grounded multidimensional metrics.^[4]

Despite these encouraging developments, major issues remain. Many of these measurements necessitate specialized

equipment, are operator-dependent, or lack standardized thresholds. Furthermore, their interpretation is complicated by ventilatory settings, hemodynamics, and metabolic state. To translate these intricate factors into effective bedside algorithms, it is essential to conduct large, prospective cohort studies that are integrated with patient outcomes. Notably, many of these indices either incorporate the $\text{PaO}_2/\text{FiO}_2$ ratio or complement these indices to support more precise, physiology-guided management. Therefore, the purpose is not to replace the $\text{PaO}_2/\text{FiO}_2$ ratio, but to contextualize it within a broader framework that includes both gas-exchange efficiency and respiratory system mechanics.

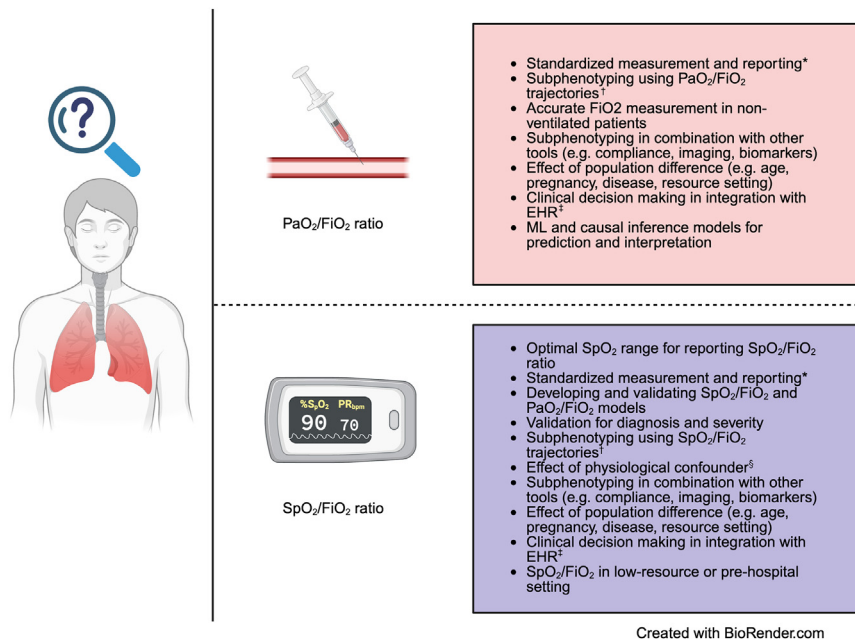
Research Priorities and the Way Forward

The limitations of current oxygenation metrics demand a systematic research agenda to develop more nuanced, context-specific approaches to respiratory assessment and care. Future investigations must move beyond simple oxygenation ratios validation toward a comprehensive evaluation of how oxygenation measures should be integrated into modern clinical practice.^[96]

The thresholds for $\text{PaO}_2/\text{FiO}_2$ ratio were established decades ago from relatively small datasets that do not reflect contemporary patient populations, ventilation strategies, or outcomes. Large-scale analyses of modern ICU databases could identify cut-offs that better align with current mortality patterns, length of stay, and resource utilization. Machine learning techniques, applied across diverse healthcare systems, might reveal that optimal thresholds vary substantially by age, comorbidity burden, or underlying pathophysiology.^[97,98] Importantly, such efforts should prioritize clinically meaningful outcomes over historical precedent, recognizing that different thresholds may more accurately predict treatment response, recovery trajectory, or the need for escalation of care.

Equally important is the recognition that universal cutoffs may be fundamentally flawed. HFNO, for example, produces unique physiological conditions in which traditional $\text{PaO}_2/\text{FiO}_2$ or $\text{SpO}_2/\text{FiO}_2$ thresholds poorly predict treatment failure or the need for intubation. Systematic studies are urgently required to evaluate oxygenation metrics across the full spectrum of respiratory support modalities, from conventional oxygen therapy and NIV to HFNO and invasive ventilation. These investigations should aim to establish context-specific thresholds that reflect the distinct physiological states created by each intervention. Patient-specific factors must also be considered. The optimal oxygenation target for an elderly patient with multiple comorbidities may differ substantially from that for a young, otherwise healthy patient with isolated respiratory failure (Figure 2).

Beyond refining thresholds, future research should move away from single-parameter assessments. Composite indices that capture the complexity of respiratory failure hold greater promise. Metrics combining oxygenation with measures of lung mechanics, such as PEEP, mean airway pressure, lung compliance and driving pressure, gas exchange efficiency, including dead space fraction, hemodynamic parameters, and inflammatory markers, could yield a more accurate and clinically useful assessment. Integration of routinely available ventilator-derived data, such as pressure–volume loops, flow patterns, or indices of work of breathing, with oxygenation measures could enhance bedside evaluation without adding invasive

**Figure 2.** Research priorities for oxygenation metrics.

EHR, Electronic health record; ML, Machine learning; PEEP, Positive end-expiratory pressure; PaO₂/FiO₂, Partial pressure of oxygen to fraction of inspired oxygen; SpO₂/FiO₂, Capillary oxygen saturation to fraction of inspired oxygen;

*Standardized measurement includes ventilator settings, FiO₂, PEEP, flow rate, patient position, time relative to intervention, vasopressors, and skin pigmentation.

[†]Subphenotyping using longitudinal trajectories of PaO₂/FiO₂ or SpO₂/FiO₂ ratios over static measurement.

[‡]Integration, automatic extraction, and validation of PaO₂/FiO₂ and SpO₂/FiO₂ from EHRs for alerts, dashboards, and research phenotyping.

[§]Physiological confounders include effect of pH, arterial partial pressure of carbon dioxide, temperature, hemoglobin, 2,3-diphosphoglycerate (DPG), dyshe-moglobinemias and cardiac output. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

monitoring.^[99] Emerging technologies, including lung ultrasound and EIT, further expand opportunities for composite metric development. Studies linking these modalities with traditional oxygenation indices may provide more reliable insight into regional lung function, recruitment potential, and respiratory reserve.

Crucially, research priorities must extend beyond the development of new metrics to their implementation in clinical practice. Understanding how different oxygenation assessment strategies affect clinician decisions, workflow efficiency, and patient comfort represents a major knowledge gap. Studies assessing the cognitive load imposed by various monitoring approaches and their influence on provider satisfaction are necessary for successful adoption.

The ultimate future of oxygenation assessment may lie not in refining individual metrics but in developing intelligent, context-aware systems that integrate multiple data streams to provide personalized respiratory evaluation. Such systems should account for patient-specific factors, treatment context, and resource constraints while maintaining the simplicity required for widespread clinical use.

In summary, the path forward involves a shift from reliance on simple, universal ratios toward sophisticated, adaptable approaches that reflect the complexity of respiratory failure. Progress will depend on combining modern analytics, advanced monitoring, and pragmatic implementation research to ensure that innovations translate into real-world benefit. The ultimate goal is to have oxygenation assessment strategies that improve patient outcomes while reducing the burden on health-care systems in an era of increasingly personalized, resource-conscious medicine.

Conclusions

Oxygenation ratios provide simple and rapid estimates of lung injury, enabling bedside assessment of ARDS severity and prognostication. They are instrumental in screening, triage, and

trend monitoring for standardized interventions. However, both metrics, PaO₂/FiO₂ and SpO₂/FiO₂ ratios, can be misleading and are highly influenced by the ventilatory settings such as PEEP, mean airway pressure, and FiO₂. The SpO₂/FiO₂ ratio is a promising alternative to the PaO₂/FiO₂ ratio, especially in resource-limited settings, but physiologic nonlinearity, FiO₂ variability, and oximetry bias limit precision around decision thresholds. There is a need for research on the validation of oxygenation ratios in diverse clinical settings, modes of oxygen delivery, and integration with other oxygenation indices, including pulmonary mechanics. Although oxygenation ratios are valuable screening and monitoring tools, they should be interpreted within the broader clinical and physiological context rather than as standalone markers of gas exchange and disease severity.

CRedit authorship contribution statement

Prashant Nasa: Writing – review & editing, Writing – original draft, Data curation, Conceptualization. **Denise Battaglini:** Writing – review & editing, Writing – original draft, Conceptualization. **Deven Juneja:** Writing – review & editing, Writing – original draft, Conceptualization. **Marcus J. Schultz:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Jozef Kesecioglu:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

Conflict of Interest

All the authors, PN, DB, DJ, MJS and JK declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Two authors are Editorial Board Members for this journal and were not involved in the editorial review or the decision to publish this article.

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